

THESIS

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CHORION-EPITHELIOMA.



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Introduction.

The problem of the ultimate cause of Chorion-epithelioma is only a part of the larger problem of the cause of the growth of living cells and of their development into complex individuals. We are still far from understanding how this normal growth takes place but we are gradually building up some knowledge of the physiological processes at work. We do not know how the cell is endowed with life, we do not know why, in the process of growth, certain cells should develop into muscle and others should form bone and nerve tissue, but we do know that it is possible to bring influences to bear on the growing cell by which its development may be encouraged or inhibited.

It has been found that, by choosing suitable culture media, we can cause an extraordinary proliferation of such primitive types as bacteria and fungi: in more complex individuals it has been shown that local injury is followed by unusual activity on the part of the cells, directed towards repair: it has been proved that excess or insufficiency of certain internal secretions is capable

of causing abnormal growth to take place in various parts of the body, and that variations in development, both local and general, may follow on variations in the diet, habits, or environment of the individual.

It was long ago recognised that although, normally, all the cells which go to make up the individual are subservient to the needs of the complex being of which they form a part, yet they possess a life of their own, so that it is possible for some of the cells of the body to die while still attached to the living being, and it is possible also for the part to live for a time even when separated from the body.

Because of this property of separate life, skin-grafting, bone-grafting, and other surgical operations of great importance have been rendered possible; and because of this same property we cannot be surprised that at times groups of cells revert to a semi-independent life and form a colony whose main function is that of propagating their own kind without reference to the needs of the body from which they derive their life. So long as this colony is isolated and does not encroach unduly on the tissues of the individual,

no harm is done, but if the colony penetrates into the normal tissues and develops malignant characteristics, then it is capable of doing very grave injury.

It is as yet impossible to explain with any certainty what causes induce special groups of cells to form these colonies or tumours, or why one group should remain innocuous to the host while another develops signs of malignancy.

It still remains an open question whether the cause lies in the potentialities of the cells themselves, or in some external influence which is brought to bear on them. There are experts who incline to the theory that tumours as a whole develop from embryonic rests - groups of cells of a primitive type which have been isolated in the body and lie latent for varying periods before developing their power of semi-independent growth: there are others who believe that the cells are of normal type, but are stimulated, either by injury or by an infective organism, or in some other way, to develop an abnormal mode of life. It is generally accepted that, in certain cases, injury is a predisposing factor - as notable examples are cancer of the tongue following

ulceration, and cancer of the cervix of the uterus, following birth injuries. The relationship of infection to tumour formation is not so certain.

It is known that infection by certain specific organisms may produce a proliferation of tissue strongly resembling tumour formation, as in the case of gumma, and attempts have been made to isolate specific germs from cancer: so far, however, no definite causative organism has been identified, although Dr. James Young has recently reported the cultivation of fungus-like bodies from cancer. Infective conditions show a tendency to spontaneous recovery - tumours show no such tendency: in infective conditions too those who are in a bad state of health are attacked more readily, whereas, although a tumour ultimately reduces the strength of the patient, it is rather more liable to attack those who are otherwise healthy. The particular form of tumour known as Chorionepithelioma resembles infective conditions in that it tends to attack those in poor health, and that it does sometimes spontaneously disappear.

History.

With the development of the microscope has come the differentiation of "cancers" into

Sarcomata and Carcinomata and the recognition of many other varieties of tumour, but it is only within the last thirty years that the true nature of Chorion-epithelioma has been recognised. It was formerly regarded as a type of Sarcoma and it was not until 1889 that Sanger first described it under the name of Deciduoma Malignum as a tumour evolved from the tissues of the pregnant uterus.

Within the next few years numerous cases were described and various theories were brought forward as regards its origin. Pestalozza in 1891 laid stress on the fact that the placental tissues were capable of giving rise to malignant tumours at the placental site or elsewhere in the body: attempts were made to distinguish between "placentoma" and "chorioma": Marchand, in the same year, showed that the tumour tended to invade the blood-vessels: Neumann and other observers emphasised the relation between the tumour elements and the chorionic epithelium and villi.

The attention of gynecologists having been directed to the tumour it was not long before other important histological studies were published. In 1895 Fraenkel suggested that the name Syncytioma Malignum would be histologically

correct. Whitridge Williams pointed out that both the syncytial layer and the Cell layer of Langhans were represented in the tumour; and Marchand drew attention to the resemblance between the tumour and the apparently dissimilar Hydatidiform mole, pointing out that in both cases there were similar cell elements and similar infiltration of the maternal tissues.

Marchand considered that the growth could occur only in connection with pregnancy, but this has been disproved by the publication of various cases in which an exactly similar tumour was found to be present in the male and in females where there was no possibility of pregnancy. Schlagenhauer in 1902 and various later observers found chorion-epitheliomatous tissue in connection with teratomata of the testis; cases were recorded as having occurred in the male in the retro-peritoneal glands, and in the glands of the mediastinum; and Breus recorded a malignant hydatid mole in the testis with secondary tumour of the heart.

Pick had several cases of ovarian chorion-epithelioma - probably associated with teratomata - one in a child of nine years, others in young girls of sixteen and seventeen.

The recognition of the type of chorion-epithelioma which is associated with teratomata helped to establish the foetal origin of the tumour: for, at the time when Marchand first demonstrated the presence in the tumour of cells representing both Syncytial and Langhaus' layer, it was the accepted opinion of the day that the chorion was partly foetal and partly maternal in origin and experts found some difficulty in accepting the theory that both maternal and foetal tissues could enter into the formation of the tumour. In time, however, the difficulty disappeared as the chorion was demonstrated to be entirely foetal in origin.

Later researches have been undertaken in order to discover some method of estimating, by histological means, the malignancy of the tumour, which varies very considerably in different cases.

Neumann believed that it was a sign of malignancy to find the stroma of the chorionic villi invaded by epithelium: Voigt considered that malignancy was indicated by an unusually marked proliferation of the cells of Langhaus' layer: later workers support this theory, laying special stress on the finding of many islands of

these cells between the muscle tissues and on the finding of many cells showing mitotic figures. None of these signs however are conclusive and it remains a difficult problem to judge of the degree of malignancy in any given case.

Pathology and Appearances.

The site of primary chorion-epithelioma is in the great majority of cases that of a recently evacuated placenta or ovum, and therefore it is most commonly found in the uterus. In this position it usually consists of an intra-mural portion, which is fairly well circumscribed, and a portion which projects into the uterine cavity like a fleshy mole. From both of these portions there is danger to the patient - the intra-mural part may enlarge until it forms a soft plum-coloured swelling projecting on the peritoneal surface of the uterus; it may perforate spontaneously and cause death by haemorrhage, or it may form troublesome adhesions with adjacent organs - if growth takes place in the direction of the bladder, it may penetrate into the bladder producing haematuria and fistula. The portion which projects into the uterine cavity, owing to its exposed situation, tends to break down and ulcerate

and forms a nidus for septic infection which may cause death from ~~from~~ toxæmia. Even if ulceration does not take place, there may be severe and dangerous hæmorrhage.

As it is possible for the ovum in any situation to become the seat of ^{Chorionic} chronic degeneration the tumour may occur in connection with an Ectopic Pregnancy, in the Fallopian Tube or the ovary. In this situation the tumour may attain a large size, it is generally covered with peritoneum, and, on abdominal section, appears as a dark plum-coloured, nodular, circumscribed tumour with a glistening capsule - it may be found burrowing deeply into the retro-peritoneal tissues at the point of attachment but, where covered with peritoneum, adhesions are generally slight and easily separated.

The danger to the host in this situation is from hæmorrhage, from secondary anaemia, and from the metastases and general cachexia which are associated with any malignant tumour.

As has already been mentioned Ch-Ep may develop from foetal tissues which occur in the form of teratomata, and the testis and ovary are the most common situations for this type.

The vaginal wall is however the most common situation for either primary or secondary chorion-epithelioma arising outside the placental site and it is in this situation that the tumour is most easily observed. It first appears as a ^{small} ~~very~~ plum-coloured nodule not unlike a thrombosed vein, but, if untreated, it may attain a considerable size and cause danger to life by severe haemorrhage, ulceration and septic infection.

Metastatic deposits occur in other situations, but these are not as a rule accessible to direct examination during life.

On section, the tumour presents a mottled appearance - it is mainly composed of blood clot which appears as dark red areas, separated from one another by paler strands of necrotic tissue. The actively growing part is at the edge and it is here that the typical microscopic characters are to be looked for. These are -

- (1) Multinucleated and vacuolated masses of protoplasm of various shapes and sizes, similar to the syncytial layer of the normal chorionic epithelium.
- (2) Masses of polyhedral cells, similar to the masses which occur at the tips of the villi of

^{the}
~~its~~ normal placenta as offshoots of Langhans' layer. They differ from the normal in having no protective "fibrinoid" layer separating them from the maternal tissues: in the later stages the cells grow larger and show mitotic figures.

- (3) Giant cells of varying size, found at points where the normal tissues are being invaded, and often found to have penetrated deeply into the maternal tissues growing along the course of the blood vessels and finding their way under the endothelium of the vessels.

The histological researches of Von Spee, Teacher, Benecke and others have given us much information as to the method of implantation and development of the normal ovum and the essential similarity of the tumour to the normal ovum has been established beyond question.

The normal chorion consists of two layers - a cell layer, and a plasmodial layer, represented in the tumour by the elements already referred to. The normal ovum erodes the maternal tissues by means of plasmodial offshoots; its villi are attached to the maternal tissues by clumps of cell islands; buds of syncytium are found as giant cells not only in the uterine tissues, but also

in distant parts of the body to which they have been carried in the circulation; whole villi in fact may be carried away and deposited in distant tissues but after a time these foetal elements are absorbed and disappear.

The tumour behaves in a similar fashion but the process goes on until pathological results ensue. Normally the process of erosion of the maternal tissues is arrested by the absorption of the giant cells, and by the formation of the placental blood sinuses in which the maternal blood meets the foetal tissues and provides for the nourishment of the ovum. In the case of the tumour, the maternal blood-vessels are more freely opened up, haemorrhage takes place into both maternal and foetal tissues, the giant cells proliferate in their new situations and produce secondary growths similar to the original one from which they are derived.

Etiology. Initiation of Tumour growth.

In some respects, as has already been shown, our knowledge of Chorion Epithelioma is further advanced than is our knowledge of other tumours, for it has been proved to be derived in most cases from embryonic cells of a definite type,

whereas in the case of sarcoma and carcinoma opinion is still divided as to the type of cell from which the tumour arises. With regard to the occurrence of Chorion Epithelioma in the male various possibilities have been suggested - Virchow believed that the cells of the testis (the usual site of the tumour) could undergo ~~meta~~ metaplasia and take on an abnormal development bearing some resemblance to the normal growth of the ovum. Marchand suggested that as the Polar bodies were extruded during the development of the sperm cell, they ^{might} ~~may~~ be stimulated to abnormal growth. It has been suggested that it may be derived from vestigial structures such as the Wolffian Body or Mullerian Duct; or that the theory of the inclusion of foetal rests may be applied to this type of tumour as well as to others. At present the most generally accepted theory is that they are derived from cells whose normal development into spermatogonia has been suppressed but whose potencies remain intact.

Where the tumour occurs in the female, in connection with pregnancy, there is no doubt as to the type of cell from which it arises:- normally the ovum goes through a process of

maturation and fertilisation and proceeds to develop according to physiological laws: abnormally, the growing cells are stimulated to unusual activity, or the resistance offered by the maternal tissues is diminished, the physiological process becomes a pathological one, and a tumour is formed. Symptoms do not generally appear until abortion or labour has taken place, but a few cases have been diagnosed during pregnancy on the appearance of a metastatic growth in an accessible site such as the vagina.

Fink has lately issued a paper in which he suggests that such growths may come into being during the earlier part of pregnancy when both the syncytium and the cell layer of the Chorionic epithelium are most active: hydatidiform degeneration of the chorion generally occurs in the early months, showing that there is a tendency to malignant proliferation at this period. Since there must always be some cause for the abortion which so often precedes Chorion Epithelioma it is quite a feasible theory that the disease had actually begun before the abortion took place. The ovum being killed by excessive haemorrhage and necrosis, the uterus expels it as a foreign body, but, as its

villi have already begun to eat deeply into the tissues, it is not entirely expelled, and so develops into a tumour.

The fact that tumour growth in a fairly large proportion of cases, follows on hydatidiform degeneration of the chorionic villi, and that in some cases there is evidence of the chorionic epithelium invading its own stroma, points to the existence of a factor affecting chiefly the growing cells, and perverting their activity.

It is probable however that a more important factor is failure of maternal resistance. In some cases there is evidence that the health of the patient has been undermined and the tissues devitalised by the circulation of toxins or by some disturbance of the general metabolism. In some cases secondary tumours have been known to disappear on the removal of the primary one, probably because the circulating toxins are diminished and the tissues are thus enabled to form a barrier against the remaining growths.

Normally, there is a protective fibrinoid area separating the ovum from the maternal tissues, and limiting its encroachment: in cases which become malignant there is evidence that the

protective layer is diminished or absent. The occurrence of Ch. Ep. degeneration in ovarian pregnancies has sometimes been regarded as such a very remarkable coincidence that attempts have been made, where possible, to find another explanation, such as possible foetal rests or teratomata. The ovary, however, is an organ readily prone to degeneration: its tissues are not built to resist the growing ovum, and, if failure of maternal resistance is one of the important factors in the development of the tumour, then there is little wonder if we do occasionally meet with this "extremely rare form of chorionic degeneration engrafted upon an extremely rare form of pregnancy".

Evidence of successful maternal resistance is to be found in the fact of the normal disappearance of the chorionic fragments which are carried during pregnancy to distant parts of the body. Also, the failure of this normal maternal resistance seems to be the most reasonable explanation of those chorion-epitheliomata which arise as apparently primary growths outside the placental site.

In connection with these extra-placental growths the theory has been put forward that the placental tissue, which has finally been wholly

expelled, was malignant when in utero and that therefore the placental fragments were malignant before they established themselves in the new site.

Although there has been an admitted difficulty in accepting the idea that such a malignant tumour could be spontaneously expelled, one cannot deny its possibility, especially since the spontaneous disappearance of both primary and secondary growths has been known to take place.

Probably however the true explanation lies in the lasting potentiality of growth present in all the embryonic cells derived from the fertilised ovum. These cells are carried in the blood stream to various parts of the body or they may pass in discharge from the uterus to the vagina and implant themselves on the ulcerated vaginal mucosa; and although they are treated as foreign substances and are generally absorbed, it is not difficult to imagine that an increase in their activity or some condition which interferes with the local resisting powers, may result in some of these metastases developing into tumours, while the majority disappear entirely.

Influence of Sex and Age.

The disease is mainly a disease of women of the child-bearing period. The tumours found in males and in female children have a different origin, arising from embryonic cells included in the testis or ovary, or from cells which, in process of maturation, develop abnormally. In the male, these inclusions tend to become active at a rather later date than is the case with the female. Pick has recorded a case of Ovarian Ch. Ep. in a female child of nine years, while no case has been recorded in a boy under the age of puberty. The secondary sex characters of the female however, tend to appear earlier than those of the male and probably the cell inclusion does not take on active growth until the parent structures become physiologically active.

Chorion-epithelioma

With regard to the typical Ch. Ep. of adult women which is associated with pregnancy, it may occur at any period of fertile life: the average age is about thirty-three, but cases may occur in young people, in connection with a first pregnancy, as well as in older people who have passed the menopause. Within the limits of the child-bearing period, the actual age of the patient does not seem

to be a factor of great importance. The degree of fertility and the nature of the preceding pregnancy are more important.

Relation to Pregnancy.

Only about five per cent of cases have occurred in connection with a first pregnancy, whilst about thirty-eight per cent have occurred in women who have had five or more children, and in whom the power of resistance has been lowered by repeated pregnancies. Other conditions such as the toxæmias of pregnancy, which lower the general health, may render the patient more liable to the disease, for in this respect chorion-epithelioma is more like an infective condition than a carcinoma or sarcoma.

As regards the nature of the immediately preceding pregnancy, Hydatidiform Mole was present in 36.6% of the 75 cases collected by Teacher, and in 48% of Hitschmann's series of 240. 31% followed abortion, and only 21% were preceded by a normal pregnancy.

Sometimes a history is obtained of previous abnormal labours: adherent placentae and retention of portions of placenta and membrane may occur in several successive pregnancies and may be the precursors of malignant growth.

In some cases there has been an increase of lutein cells in the ovaries, with the formation of lutein cysts, and it has been suggested that the cause of the tumour may be found in this extraordinary lutein activity. It has not been established however that there is any causative connection between the two, although it is highly probable that both are at least the result of the same ultimate cause and indicate the presence of metabolic changes in the individual economy.

A few cases have been recorded in which the disease was found to exist during pregnancy - Pick, in 1897, found a vaginal chorion-epithelioma associated with a hydatidiform mole and Walthau found a similar condition in an apparently normal pregnancy. In the majority of cases, however, there is a definite interval between the termination of pregnancy and the onset of the symptoms of disease. In some cases the interval is extremely short; usually it is a few weeks; occasionally it has been some months or years.

In many cases where the interval is a long one it is difficult to say whether there has been an early abortion or not: a short period of amenorrhoea followed by a "menstrual period" of

more severity than usual, accompanied by discharge of clots is often taken as a probable indication of abortion, but proof is very often lacking.

Chorion-epithelioma having arisen in women who had not menstruated for some years and in whom there had been no indication of abortion, it came to be generally accepted that chorionic cells might remain latent in the tissues for a long time before taking on active growth. The chorionic epithelium is however normally so short-lived when separated from the ovum, that this long period of latency has been called in question - it has been shown that pregnancy may occur after the cessation of menstruation, and it seems most probable that in those cases where a long interval has elapsed since the last recognized pregnancy, there has been a more recent unrecognized early abortion.

Clinical Features.

Before discussing the clinical features of the condition I shall give a short account of four cases which I was fortunate enough to see when in residence at a Hospital for women, in 1920.

Case I. Mrs. A---, a multipara, aged 43, was admitted on the 12th. May 1920.

She had ten children, the eldest 20, and

the youngest 2 years of age. On the 2nd February, after having missed one menstrual period, she had a severe haemorrhage, and a diagnosis was made of early abortion.

The haemorrhage continued, and she became progressively weaker, until finally the doctor sent her into hospital for exploration of the uterus.

On admission she was very ill, there was marked secondary anaemia, the temperature was swinging (varying from 99 to 101°). She complained of constant pain in the back and in the lower part of the abdomen, and suffered from frequent vomiting and faintness.

On examination, a brownish-purple smooth nodule, about the size of an almond, was found on the anterior vaginal wall. The uterus was slightly enlarged and tender, was freely movable and in normal position.

On the 13th May, the vaginal tumour was removed under local anaesthesia, the os was dilated, and a soft friable mass taken with ovum forceps from within the uterine cavity.

Both specimens were sent for microscopic examination and were reported to be typical Chorion Epithelioma.

The patient improved to some extent after the exploration and was very unwilling to have a radical operation performed. She finally agreed to it however, and a Panhysterectomy was done on the 3rd. June.

The main growth was embedded in the posterior wall of the uterus, bulged outwards under the peritoneal coat, was about 2" wide and communicated with the uterine cavity by a small opening of about $\frac{1}{2}$ " diameter through which a piece of the tumour projected like a polyp. There were two small growths in the uterine wall, about $\frac{1}{2}$ " distant from the main one, and the muscle of the uterus was extremely white and showed some fibrosis.

No other secondary deposits were found at the operation, and the patient made an excellent recovery although, owing to the anaemic condition, convalescence was somewhat protracted. She was quite well six months later.

Case II. Mrs. W---, a multipara, aged 38, was admitted on the 6th. June ~~under the microscope~~ She had had four children, then four miscarriages (the last miscarriage had taken place at the fourth month of pregnancy, about six weeks before).

There was a history of venereal disease

(Syph: and Gon:); menstruation had been excessive, and occurred fortnightly for some years before; there had been intermittent loss during pregnancy, and constant loss since the abortion took place.

On examination the uterus was found to be bulky and tender, the ovaries were slightly enlarged, and there was an offensive red discharge. The os was not closed, and a soft mass could be felt with the finger.

On the 9th June, the uterus and adnexa were removed. There were no adhesions and no secondary nodules found at the operation.

On section, the uterus was found to contain an irregular, haemorrhagic growth about the size of a plum, arising from the fundus and from the upper part of the posterior wall.

An outlying nodule of growth was found in the uterine wall at some distance from the primary tumour.

The patient made a good recovery.

Case III. A.H. a primipara, aet. 21, was admitted ~~under the same name~~ on the 13th May.

There was a history of 10 weeks' amenorrhoea, followed by haemorrhage and sickness of three weeks' duration.

The uterus had increased in size very rapidly, and, on admission, was the size of a 7-months' pregnancy .

On the 14th the cervix was dilated and a hydatidiform mole expelled. For a week after the expulsion of the mole the temperature remained normal, although the pulse varied from 100 to 128. On the 21st. the temperature rose to 100°, the patient complained of pain on micturition, and there was some albuminurea, which disappeared within a few days.

From the 21st. to the 28th. the temperature rose to 100° each night, there were some shivering attacks, and some abdominal pain - sometimes of a colicky nature, sometimes localised to the right iliac region.

The uterus was still large (about the size of a 4-months' pregnancy), the ovaries were palpable and there was slight vaginal discharge.

On the 5th June the ovaries were much larger and felt cystic, the right ovary was felt as a definite mass in the lumbar region, nearly at the level of the umbilicus. The ovarian cysts continued to grow rapidly, the uterus was still larger than normal, and remained tender on pal-

pation. Slight vaginal discharge appeared again on the 14th. June.

^{diagnosis}
A ~~diagram~~ was made of chorion-epithelioma and lutein ovarian cysts and a radical operation was performed on the 15th June.

The uterus was enlarged and soft (the size of a pregnancy of $3\frac{1}{2}$ months) a purplish area was noted in the anterior wall, but there was no definite localised swelling.

The right ovary formed a thin-walled cyst about the size of a melon, and had a twisted pedicle: the left ovary was also cystic and was enlarged to the size of an orange. No enlarged lymphatic or secondary nodules of growth were observed.

The uterus, tubes and ovaries were removed. On section the uterine wall was found to be $1\frac{1}{2}$ " thick: it was very soft and the endometrium was thick and congested. Groups of vesicles were attached to the uterine wall near the internal os and there were also a few isolated vesicles near the fundus. A small circumscribed, dark-coloured tumour (of about 1" diameter) was found embedded in the anterior wall but communicating with the uterine cavity although not projecting into it.

The tubes were normal: the specimen was kept for museum purposes and accordingly no microscopic examination of the ovarian cysts was made — a section of the tumour on examination showed the typical character of chorion-epithelioma.

The patient made a good recovery.

Case IV. Mrs. M. Aet 25, was admitted on the

6th of May complaining of a rapidly growing, tender, abdominal swelling. She had one child aet. 2 years; pregnancy and labour had been normal.

History - Amenorrhoea of 14 days in January 1920, followed by a menstrual period which lasted 14 days and was initiated by a severe attack of abdominal pain accompanied by vomiting. There was no menstrual period in February, menstruation was normal in March and absent again in April and May. The abdominal swelling had been observed for about a month.

On examination the uterus was found to be fixed, and not enlarged, a large nodular, cystic and very tender mass was found rising out of the pelvis and extending to level of umbilicus.

Ectopic pregnancy was suspected and operation was undertaken on the 7th May. On abdominal section a large, nodular, haemorrhagic tumour was

found rising out of the pelvis, behind and to the right of the uterus: it was plum coloured, covered with peritoneum, not adherent to intestines, but closely adherent to the lateral pelvic wall and to uterus and Pouch of Douglas; the tube was intact and spread out over the growth which occupied the position of the right ovary. The left tube and ovary were normal. The tumour was removed along with the uterus, tubes, and left ovary, and on examination was found to be a typical Chorion-epithelioma.

No secondary tumour was discovered, and in spite of the fact that, as the pelvic tissues were deeply infiltrated, it was impossible to remove the whole of the growth, the patient made a good recovery and remained well for some months.

In December however, she was re-admitted with a recurrence of the condition.

On this occasion she was extremely anaemic, her general health was poor, and there were signs of the lung being affected. Laparotomy was undertaken, but the tumour, which had reached a larger size than the original one, was more closely attached to the intestines and had spread more deeply into the parietal tissues, and complete

removal was impossible.

The patient died the same day and secondary growths were found Post Mortem in the liver and in the lungs.

Analysis of the Cases :-

These four cases although they do not bring to light any new facts, formed an interesting series for study.

As regards Etiology, all were apparently connected with pregnancy and in no case was the immediately preceding pregnancy a normal one, - there was no absolute certainty of an early abortion having taken place in Case I, but it was at least extremely probable. In Case IV also one can only surmise as to the pre-existence of an ectopic pregnancy, but on the whole, the clinical features pointed to this condition.

It is of course possible that the early haemorrhage in January might be due to an early abortion and that the ovarian tumour might arise as a metastatic growth: in consideration of the fact that apparently primary tumours occur in the vagina and in other situations while the uterus remains unaffected, this possibility cannot be ruled out, but, as ovarian pregnancies have been

known to occur it seems at least as likely that the tumour originated in this way. Another possibility is that the condition might have arisen from a teratoma of the ovary but this is also a rare condition.

Two of the patients were multiparae who had had more than the average number of pregnancies and were approaching the end of the fertile period : - in the case of the older of the two, there was no history of previous difficult labours; the younger one had been in bad health during the four months of pregnancy and for some time before, and the last four pregnancies had terminated in abortion.

In the case of the young primipara, the preceding pregnancy was Hyd: Mole.

Thus as regards the effect of the age of the patients, the nature of the immediately preceding pregnancy, and the degree of fertility, these cases bear out the generally accepted principles referred to in discussing the Etiology.

1. The symptoms may be divided into three groups
 1. "Those due to the local condition"
 2. "Those due to its effect on the general health"
 3. "Those due to the development of secondary growths."

We have, first, those which are directly referable to the primary tumour. Pain has not generally been regarded as a cardinal symptom, and it is interesting to note that it was a feature of all four cases recorded above: the local tenderness is probably due to the stretching of the tissues by haemorrhage: backache and general abdominal pain may occur as the result of congestion - in the second case noted above the pain was stated to be an exaggeration of the usual menstrual pain which was of the congestive type: in Case III, there was a distinct local tenderness on pressure over the uterus, and later came the colicky type of pain which might be attributed to the twisted pedicle of the ovarian cyst.

Haemorrhage is generally regarded as the earliest and most important sign. One expects to have a certain amount of haemorrhage following labour or abortion, but this should rapidly lessen, and, if it continues beyond the normal period of the puerperium, or if it is excessive in amount, one should regard it as a sign of great importance. In Case I. there was a history of three months' haemorrhage, in Case II., of six weeks, before the patient was admitted to Hospital. In Case III.

there was practically no haemorrhage in the three weeks which elapsed between the two operations, but the growth was a very early one and had hardly begun to involve the uterine mucosa. In Case IV. the local haemorrhage taking place into the tumour, merely added to the size of the tumour, but there was in addition an intermittent uterine haemorrhage (probably due to congestion) which suggested the possibility of Ectopic pregnancy. With the breaking down of the tumour in exposed situations comes the liability to septic infection, with offensive discharge locally, and toxic symptoms generally.

As a result, partly of the haemorrhage and partly of the general intoxication, constitutional symptoms arise. Anaemia is common, with its attendant evils of faintness, muscular weakness, and intestinal disturbance. If septic infection has occurred there is irregular pyrexia. Wasting may occur but is not constant, except in the late stages of the disease.

A third group of symptoms is due to the occurrence of metastasis. The establishment of a new focus in any position may give rise to rigors and pyrexia. There may be haemoptysis

or signs of consolidation or effusion from involvement of the lung, one case has been recorded in which the characteristic cells were found in the sputum: Convulsions or paralysis or other nerve symptoms may appear as the result of tumour formation in the brain. Haematuria may follow spread of the tumour to the bladder or kidney.

In these four cases there were only two in which the presence of metastasis was definitely diagnosed: in the first case, the secondary growth was visible in the vaginal wall. Metastases were found in two cases in the uterine wall showing that the tumour cells are like normal syncytium in finding their way into the substance of the uterus.

Diagnosis.

In the case of Chorion Epithelioma occurring in the male no diagnosis can be made except by microscopic examination of the tumour. In the case of Chorion Epithelioma associated with pregnancy, although the final diagnosis depends on microscopical examination, yet the condition is as a rule suspected before such examination is undertaken.

The condition has been recorded as occurring

during pregnancy, but the diagnosis has only been made when the tumour is found in an accessible position, such as the vagina.

After abortion or labour if a routine examination is made at the end of three weeks, one finds some indication that the puerperium is not quite normal: subinvolution, or undue tenderness over the uterus, or excessive haemorrhage, ~~ef~~ or offensive and prolonged lochia, are all indications for careful examination: they may be due to mild septic infection, or to retained products of conception, or to the presence of benign tumours such as fibroid or adenoma, but the possibility of Chorion Epithelioma should always be kept in mind, and steps taken to ensure that a correct diagnosis is made by means of the microscope.

Features in the history which would make one strongly suspect tumour have been mentioned under etiology. If the patient is a woman who has borne many children, if the preceding pregnancy was a Hyd: Mole, if there is a history of difficult or abnormal labours, or of toxæmia during pregnancy, then we know that there is some predisposition to the disease. In such a case it is necessary to use great care in obtaining

curettings for examination, for rough handling may not only cause severe and dangerous haemorrhage or perforation of the uterus, but it may set up metastases in other parts of the body and render cure impossible.

Although in most cases there is a definite clinical relationship between the onset of the disease and a previous pregnancy, yet it is important in diagnosis to remember that many cases have now been recorded in which there is no history of recent pregnancy. Chorion epithelioma may occur after a very long clinical interval even in women who have passed the menopause, either as the result of an unsuspected pregnancy or as the result of some stimulus applied to embryonic cells which have remained latent during a long interval. In such cases when symptoms of haemorrhage, pain, and offensive discharge occur, one naturally suspects the presence of cancer, and a thorough examination is undertaken. It is important to distinguish between cancer and chorion epithelioma for, since ~~chorion-epithelioma~~ ^{chor. ep.} has little tendency to invade the lymph glands, the type of operation chosen will depend on a complete diagnosis being made.

Taking the symptoms individually we find that none of them are pathognomonic.

Haemorrhage, which is generally the first complaint, is one of the most common complaints in women. Irregularities in menstruation may occur with no discoverable pathological condition. Any pelvic congestion or uterine tumour or abortion or ectopic gestation may give rise to it, and the diagnosis based on clinical features alone must be regarded as only probable.

Offensive discharge, which very often follows the definite haemorrhage, may occur from any infection of the endometrium - as a rule the surface of the uterine wall has been injured by pregnancy or ulceration and septic organisms have gained entrance, so that offensive discharge may indicate puerperal sepsis, or gonorrhoea, or sloughing and ulcerating tumour.

Pain is a very common accompaniment of all pelvic congestion. It may occur in cases of Chorion Epithelioma but is not invariably present. Tenderness over the site of the tumour is more characteristic and should help to distinguish the condition from sub-involution due to simple retention of products of conception.

The constitutional symptoms too are indeter-

minate. Anaemia and intestinal disturbances may follow haemorrhage from any cause - menorrhagia, ^{haemorrhage} ~~haemorrhage~~ complicating ~~of~~ labour, fibroids or cancer may all produce constitutional disturbances varying, not according to the exciting cause, but according to the period of time for which it has acted.

Irregular pyrexia indicates, as a rule, septic absorption, and may accompany ulceration or sloughing from any cause such as the breaking down of simple or malignant tumours, ulceration of the vaginal wall or cervix, or infection of the placental site during the puerperium.

Rigors may indicate the establishment of fresh metastases, but they may equally indicate the establishment of fresh foci of infection in septicaemia.

Curettage as a means to diagnosis :-

When curettage is undertaken for diagnostic purposes, it is important not to be misled by the feeling of the inside of the uterus - in most cases the protruding mass is easily removed, and the wall of the uterus is left smooth and uniform, differing in this respect from cases of carcinoma in which a rough area remains after curetting.

If the protruding portion of growth is removed, there is often some temporary improvement in the condition of the patient, owing to the diminishing of haemorrhage and septic absorption, but the growth usually recurs within a few weeks, whereas, in the case of simple retained placenta the improvement is lasting. This rapid re-formation of tumour after clearing out the uterus is characteristic and ought to be taken as diagnostic of Chorion-epithelioma.

If, however, the practice is made of submitting all curettings to microscopic examination, the diagnosis ought to be made without waiting for a return of the condition.

If a definite tumour is present and part of its growing edge is obtained for examination, diagnosis is comparatively easy, the necrotic tissue and blood clot, with Syncytial masses and cell islands, forming a typical picture. When, however, the specimen for examination is got by curetting, it may be very difficult to say whether or not there is malignancy.

If complete and apparently normal chorionic villi are present, then the condition is probably one of simple retained placenta.

If there is no definite arrangement of the chorionic epithelium in layers, if the epithelium is found to be invading the stroma, if the cell layer shows undue proliferation and undue penetration into the muscle cells, then the probability is that the condition is malignant. The cell elements are so characteristic that there is no difficulty in diagnosing the condition from carcinoma and sarcoma.

It is still difficult, however, to give an absolutely certain diagnosis and there is no doubt that mistakes are sometimes made if one depends on microscopic evidence alone:- In one case recorded by Graefe in 1902 operation was delayed because apparently normal villi were present, and the case ended fatally. In another case which was apparently Ch-epithelioma following hydatid mole, operation was delayed for the same reason, and the patient recovered; and other cases have occurred in which curettings were diagnosed as malignant and on operation the uterus was found to contain remains of a simple ovum.

Differential Diagnosis.

Other conditions which give rise to the same clinical picture as Ch.-epithelioma are incomplete

abortion, sub-involution due to retention of products of conception, sloughing fibroid, Carcinoma or Sarcoma of body of uterus, puerperal sepsis.

In most of these one has to be content with a "probable" clinical diagnosis, based on a consideration of the history of the case, the age, degree of fertility, history of pregnancies, presence or absence of metastases. In the absence of a visible or palpable growth physical examination gives little help, for haemorrhage, offensive discharge, and enlargement of the uterus occur in all cases, and curetting is generally undertaken in order to establish the diagnosis.

Although at present, many experts are opposed to examination of the interior of the uterus in cases of puerperal sepsis, I believe that it ought to be done in order to avoid the possibility of leaving palpable septic masses inside. As a rule, such examination would discover the presence of a new growth, but in the case of tumours commencing deep in the uterine wall and co-existent with sepsis, it is possible, even if careful examination is made, to miss the condition.

Chorion-epithelioma in unusual situations,

such as the Fallopian tube or ovary, is as a rule diagnosed as ectopic pregnancy. Apart from the signs of ectopic pregnancy, the only sign which might raise a suspicion as to the true nature of the tumour, is the possible rapidity of growth, but the diagnosis is only established when operation is undertaken.

Chorion-epithelioma arising in a patient who is past the menopause is liable to be mistaken for cancer. Where any doubt exists the diagnosis should be cleared up by microscopic examination, for, although operation is indicated in both cases, a more extensive operation is usually necessary in the case of cancer which is apt to spread to the lymphatics at an early stage.

Prognosis and Treatment :-

There is no disease in which the ultimate result is less certain than in the case of Chorion-Epithelioma. There are very marked variations in malignancy, and cases which appear to be clinically almost identical, frequently give very different end results. The cases of Chorion-Epithelioma of the ovary reported by Mr. Fairbairn and Mr. Phillips (case IV above) were remarkably alike - both women were 25 years of age, neither had had a large number of pregnan-

-cies, in both cases the tumour was of approximately the same size, in both the operation was necessarily incomplete because it was impossible to clear out the tumour tissue at the pelvic brim, both patients made a good recovery from the operation but in one case recovery was permanent whilst in the other there was recurrence and death within six months.

Other parallel cases could be cited:- Pick reports that a vaginal chorion-epithelioma was found in a woman of twenty who shortly after expelled a hydatid mole from the uterus: the tumour was excised and the patient recovered. A similar vaginal tumour was found in a patient of Peters' three days after the expulsion of a hydatid mole: the tumour was excised but recurred in seven months and death ensued. In Peters' case operation was delayed for six weeks, but this is not sufficient to account for the different end-result, for in a similar case of Von Guerard's where operation was delayed for $2\frac{1}{2}$ months after the onset of symptoms, the patient recovered.

In most cases early operation seems to offer the best chance of cure, and yet the interval between the onset of the symptoms and the performance

of the operation has not been found to be of any very great value in prognosis. In the statistics published by Teacher in 1903 the average interval in 50 cases of recovery was $4\frac{1}{2}$ months, and in 32 fatal cases, 4 months.

In one case of recovery the interval had been 14 months, and several cases have been published in which operation was not performed and yet the tumour disappeared and the patient recovered. Thus, Hitschmann records a case in which operation was begun and abandoned because of the extensive involvement of the vagina and bladder: within a month the tumour had disappeared.

Hormann had a case of recurrence after removal of uterine and vaginal tumours, where the patient became cachectic and showed signs of metastases, and then gradually recovered.

The nature of the preceding pregnancy sometimes gives some indication as to the malignancy of the tumour. Cases following hydatidiform Mole are not as a rule of a high degree of malignancy, although, as we have seen above, some of them prove fatal. Cases following normal pregnancy are more grave than those following abortion, possibly because, owing to the abnormal size of the uterine

vessels, metastases take place more readily.

In a series of cases collated by Findley, of tumours outside the placental site, a very considerable proportion of the fatal cases followed normal labour, and he does not record a single recovery as taking place after a full-term labour. In the same series, following early abortions, he reports five recoveries and one fatal case in which operation had been delayed for seven months.

The early appearance of symptoms is generally regarded as a bad sign and yet recovery has been known to take place when metastases had taken place during pregnancy, so that there was no clinical interval: on the other hand, death followed in Wehle's case where there was an interval of six months.

The occurrence of metastases is a bad sign but, even if the secondary growths are not in an accessible situation, this is no contra-indication to operation, for the secondary growths have been known to disappear after removal of the primary one.

The natural method of cure on the few occasions when it takes place either in the primary or secondary nodules has been demonstrated by Neumann,

Teacher, Marchand and others. The tumour tissue which eats into the vessels may become embedded in thrombus, and, being entirely separated from the living maternal tissues from which it derives its sustenance, it is destroyed and finally disappears. There is always a large amount of haemorrhage and thrombosis in connection with the growing tumour, and although this is generally insufficient to destroy every portion of growth, yet, in a few rare cases, owing partly to thrombosis and partly to the reaction of the maternal tissues, complete cicatrization is brought about. The final result then depends to some extent at least on the occurrence of thrombosis or fibrosis and on such accidents as the setting free of emboli by exertion on the part of the patient or by manipulation on the part of the medical attendant.

As the large proportion of cases show definitely malignant characteristics, and we have at present no means of gauging the degree of malignancy with any certainty, the recognized form of treatment is to remove the tumour as early and as completely as possible.

The growth may be so extensive and may infiltrate the tissues to such an extent that it is

impossible to remove it entirely, and, although the remaining portion may be absorbed, it is equally possible that it may continue to grow and soon attain to its original size: very often the portion left behind is easily visible to the naked eye, but local recurrence may take place also in those cases in which no gross tumour tissue is apparent.

Another possible source of failure, apart from the dangers connected with shock and anaesthesia, lies in the fact that metastatic growths may be established by emboli set free during the operative manipulations: in order to minimise this danger, the utmost care and gentleness should be used in all intra-uterine and intra-abdominal manipulations, and precautions should be taken by early ligature of the ovarian and uterine veins, or if necessary by ligature of the internal iliacs, to close the normal channels by which emboli travel to the lungs and other organs.

The prognosis then must always be guarded; there is no guarantee against local recurrence even if the removal is apparently complete, and there is no cause for despair even when large masses have to be left behind, or when metastatic growths are present.

If the patient survives the operation for six months without any sign of recurrence, then it is probable that recovery is permanent; if she survives for two years, the case is to be regarded as cured.

According to the statistics of 189 cases published by Teacher in 1903, 63% showed immediate recovery, but only 34.2% showed permanent cure.

Operative Technique.

The operative technique does not differ materially from that of other pelvic operations.

For growths which are situated in the vagina or cervix either local or general anaesthesia may be used. The patient is placed in the lithotomy position (if necessary, slightly exaggerated), the growth, with the overlying mucous membrane, is excised, and repair of the vaginal wall carried out as in a Colporrhaphy. In some cases, the operator has taken the precaution of removing the uterus as well as the vaginal tumour, but this need not be done if the uterus is normal: it ought to be sufficient to keep the patient under close observation and be prepared to perform a radical operation should the need arise.

If the tumour involves the uterus, then hysterectomy should be done. The anaesthetic

used depends on the predilections of the surgeon and of the anaesthetist. Gas and oxygen, administered by means of Boyle's apparatus, is an excellent anaesthetic for patients who are in a weak and anaemic state.

This was used for the first of the cases recorded above, and there was no post-operative sickness or vomiting. It is however too expensive an anaesthetic for general use, and the one used for the other cases was warm Ether vapour, administered by Shipway's apparatus. This too gave good results; there is less sickness and less irritation to the respiratory tract than when open ether is used, and there is also a considerable reduction in the amount of anaesthetic required.

Beyond the administration of morphia and atropin, before operation, and the giving of Solines either during or after operation, no special precautions were taken to prevent shock.

It would be possible, if considered advisable in special cases, to block the sympathetic ganglia, or to combine spinal and general anaesthesia, but in the majority of cases this is unnecessary and chloroform or ether administered by the usual open method are quite satisfactory in competent hands.

The patient is placed in the Trendelenburg position, the incision is made in the middle line of the abdomen below the umbilicus, the organs are examined and the extent of the operation decided upon.

If the tumour is small, involving only the uterus, a simple hysterectomy may reasonably be expected to suffice. Many surgeons ~~would~~ remove the ovaries also even if they are not affected, for they are liable to give trouble later and necessitate a second operation. If, however, the ovaries are healthy and the patient is young, it seems advisable to retain them, for our knowledge of the internal secretions and the influence of the ovarian secretion on the individual economy is not yet sufficient to enable us to say that no harm is done by its removal; and even if the ovaries atrophy, as they are liable to do, the gradual disappearance of the ovarian secretion will throw a less sudden strain on the system than if the complete operation were performed at once.

If the ovaries are involved they must be removed along with the uterus, and if the tumour tissue encroaches upon the bladder or rectum or peritoneum, the operation becomes more extensive and more difficult.

Gentleness in all manipulations is of the first importance: if the tumour is localised in the wall of the uterus it is comparatively easy to complete the operation without much disturbance of the growth - the ovarian vessels and round ligaments may be clamped at once, and, when the peritoneum has been stripped back from the anterior surface along with the bladder, the uterine vessels and the leash of veins at the fornices of the vagina, may be ligatured with the minimum of handling.

If the pelvic wall is infiltrated and the growth is not completely localised, it is more difficult to guard against possible emboli, but something may be done by ligating the internal ^{if accessible} iliacs before beginning to cut into the growth.

There is always a considerable amount of free haemorrhage if the growth is infiltrating the tissues and has to be cut into. Clots should be carefully removed and the part swabbed out with ether, in order to prevent irregularities of pulse and temperature after operation due to the absorption of blood.

Even if secondary growths are known to be present in inaccessible situations such as the

lungs, liver, or brain, operation furnishes a possibility of cure, for, after removal of the primary tumour the maternal resistance may increase and the secondary growths may be absorbed.

X-Ray treatment has been found in some cases to hasten absorption and it should therefore be tried as part of the after treatment in cases with secondary tumours which cannot be removed by operation and in those cases where complete removal has proved impossible.

Summary.

Chorion-epithelioma malignum, as a definite clinical entity, occurs in women of the child-bearing period, and is closely associated with pregnancy. It is of foetal origin, being derived from, and having the same cell elements as the chorionic epithelium.

It generally arises in the placental site, after evacuation of the foetus, but it may arise in any situation to which the chorionic cells have been carried by the blood stream or in which they have been implanted by direct contact.

Factors which favour its establishment are to be found in conditions which lower the normal resistance of the maternal tissues to encroachment



by the ovum. Such are :- a high degree of fertility, toxaemias of pregnancy, intercurrent disease. It is to be looked for also in conditions which indicate chorionic degeneration or abnormality of growth or behaviour^{of the growing cells :} a series of labours in which there were adherent placentas, or the occurrence of hydatidiform mole may be followed by chorion-epithelioma.

The symptoms (pain, haemorrhage, and vaginal discharge) are indeterminate; generally the clinical picture is that of incomplete abortion, or, in severe cases, of puerperal septicaemia: and the diagnosis is made by microscopic examination.

The condition varies very much in malignancy. Spontaneous recovery has been known to take place, and secondary tumours may disappear when the primary one has been removed.

The usual course, however, if the tumour is not removed by operation, is local ulceration, haemorrhage, septic absorption, constitutional weakness, and metastases, ending in cachexia and death.

The prognosis, even after early and apparently successful operation, must always be guarded, but is especially unfavourable if the disease

appears after a normal pregnancy, if the interval between the termination of pregnancy and the onset of the symptoms is very short, if the interval between the onset of the disease and operation is unduly long, or if extensive metastases have occurred. The prognosis is better in cases which follow early abortion or hydatid mole than after a full term of pregnancy.

In all cases the correct line of treatment is to remove the tumour or tumours if possible. X-Ray therapy may be tried if the growth cannot be removed.

Unless the tumour is very far advanced there is usually at least a temporary recovery, but the patient must be kept under close observation for some months, and should return for examination at intervals, for two years before she can be regarded as free from the risk of recurrence.